Long-term outcome of primary bilateral macronodular adrenocortical hyperplasia after unilateral adrenalectomy

Oßwald, Andrea ; Quinkler, Marcus ; Di Dalmazi, Guido ; Deutschbein, Timo ; Rubinstein, German ; Ritzel, Katrin ; Zopp, Stephanie ; Bertherat, Jerome ; Beuschlein, Felix ; Reincke, Martin

Abstract: CONTEXT Unilateral adrenalectomy has been proposed in selected patients with primary bilateral macronodular adrenocortical hyperplasia (PBMAH), but its long-term outcome is unclear. OBJECTIVE The aim of this study was to analyze long-term clinical and biochemical outcome of unilateral adrenalectomy versus bilateral adrenalectomy in patients with PBMAH in comparison to outcome of cortisol-producing adenoma (CPA) treated by unilateral adrenalectomy. DESIGN Retrospective observational study in three German and one Italian academic tertiary care center. PATIENTS AND METHODS 25 PBMAH patients after unilateral adrenalectomy (unilat-ADX-PBMAH), 9 patients with PBMAH and bilateral adrenalectomy (bilat-ADX-PBMAH) and 39 patients with CPA and unilateral adrenalectomy (unilat-ADX-CPA) were included. RESULTS Baseline clinical and biochemical parameters were comparable in unilat-ADX-PBMAH, bilat-ADX-PBMAH and unilat-ADX-CPA. Directly after surgery, 84% of the unilat-ADX-PBMAH patients experienced initial remission of Cushing's syndrome. In contrast, at last follow-up (median 50 months) 32% of the unilat-ADX-PBMAH patients were biochemically controlled compared to nearly all patients in the other two groups (p=0.000). Adrenalectomy of the contralateral side had to be performed in 12% of the initially unilat-ADX-PBMAH patients. 3 of 20 unilat-ADX-PBMAH patients (15%) died during follow-up presumably of Cushing's syndrome related causes whereas no deaths occurred in the other two groups (p=0.008). Deaths occurred exclusively in patients who were not biochemically controlled after unilateral ADX. CONCLUSIONS Our data suggest that unilateral adrenalectomy of PBMAH patients leads to clinical remission and a lower incidence of adrenal crisis, but less sufficient biochemical control of hypercortisolism potentially provoking a higher mortality.

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Outcome of primary bilateral macronodular adrenocortical hyperplasia

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Andrea Oßwald[1], Marcus Quinkler[2], Guido Di Dalmazi [3], Timo Deutschbein[4], German Rubinstein[1], Katrin Ritzel[1], Stephanie Zopp[1], Jerome Bertherat[5], Felix Beuschlein[1,6], Martin Reincke[1$]

[1] *Medizinische Klinik und Poliklinik IV, Klinikum der Universität, Ludwig-Maximilians-Universität München, Germany*

[2] *Endocrinology in Charlottenburg, Berlin, Germany*

[3] *Endocrinology Unit and Center for Applied Biomedical Research, Department of Medical and Surgical Sciences, Alma Mater University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy*

[4] *Division of Endocrinology and Diabetes, Department of Internal Medicine I, University Hospital Würzburg, Würzburg, Germany*

[5] *Université Paris Descartes, hôpital Cochin, centre de référence des maladies rares de la surrénale, service d'endocrinologie, Paris, France*

[6] *Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, UniversitätsSpital Zürich, Zürich, Switzerland*

ORCiD numbers:

0000-0002-1291-8906

Di Dalmazi

Guido

0000-0003-0586-0168

Deutschbein

Timo

0000-0003-2551-3008

Bertherat

Jerome

0000-0001-7826-3984

Beuschlein

Felix

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The aim of this study was to analyze long-term clinical and biochemical outcome of unilateral adrenalectomy versus bilateral adrenalectomy in patients with PBMAH in

comparison to outcome of cortisol-producing adenoma (CPA) treated by unilateral adrenalectomy.
DESIGN
Retrospective observational study in three German and one Italian academic tertiary care center.
PATIENTS AND METHODS
25 PBMAH patients after unilateral adrenalectomy (unilat-ADX-PBMAH), 9 patients with PBMAH and bilateral adrenalectomy (bilat-ADX-PBMAH) and 39 patients with CPA and unilateral adrenalectomy (unilat-ADX-CPA) were included.
RESULTS
Baseline clinical and biochemical parameters were comparable in unilat-ADX-PBMAH, bilat-ADX-PBMAH and unilat-ADX-CPA. Directly after surgery, 84% of the unilat-ADX-PBMAH patients experienced initial remission of Cushing's syndrome. In contrast, at last follow-up (median 50 months) 32% of the unilat-ADX-PBMAH patients were biochemically controlled compared to nearly all patients in the other two groups (p=0.000). Adrenalectomy of the contralateral side had to be performed in 12% of the initially unilat-ADX-PBMAH patients. 3 of 20 unilat-ADX-PBMAH patients (15%) died during follow-up presumably of Cushing's syndrome related causes whereas no deaths occurred in the other two groups (p=0.008). Deaths occurred exclusively in patients who were not biochemically controlled after unilateral ADX.
CONCLUSIONS
Our data suggest that unilateral adrenalectomy of PBMAH patients leads to clinical remission and a lower incidence of adrenal crisis, but less sufficient biochemical control of hypercortisolism potentially provoking a higher mortality.

Unilateral adrenalectomy in primary bilateral macronodular adrenocortical hyperplasia leads to a lower rate of adrenal insufficiency, but also less sufficient biochemical control of hypercortisolism.

Main Text

INTRODUCTION

Endogenous Cushing's syndrome (CS) is a severe disease based on excessive glucocorticoid production [1]. In approximately 20% of cases cortisol is secreted autonomously by the adrenal cortex [2]. Adrenal Cushing's syndrome is mostly caused by unilateral cortisol-producing adrenal adenomas (CPA) and less frequently by cortisol-secreting carcinomas. Very rare causes are primary bilateral macronodular adrenocortical hyperplasia (PBMAH), bilateral CPAs and primary pigmented micronodular adrenal disease [3,4].

PBMAH presents on imaging with a characteristic appearance of multiple bilateral macronodules (>10 mm) with hyperplasia and/or internodular atrophy [5]. Pathophysiologically, the expression of aberrant membrane receptors in the adrenal cortex plays an important role [4]. In most instances, PBMAH is a sporadic disorder, although familial cases have been described [6]. Biallelic inactivating variants in the Armadillo repeat containing 5 gene (*ARMC5*), a tumor suppressor gene, is a frequent cause of PBMAH [7]. Characteristically, a germline and a somatic tissue-specific gene variant are required for the development of PBMAH, which is consistent with the two-hit hypothesis of tumorigenesis [8].

Treatment of choice to control hypercortisolism in patients with PBMAH is bilateral adrenalectomy, which inevitably results in lifelong glucocorticoid dependence and, thereby, risk of adrenal crisis [6]. To avoid the induction of adrenal insufficiency, resection of only one adrenal gland has been advocated. Indeed, several recent studies have reported clinical and biochemical improvement after unilateral adrenalectomy [9-13]. However, the number of documented patients and associated follow-up time is still limited. Here, we report the largest

series of PBMAH patients following unilateral adrenalectomy with analysis of long-term results regarding biochemical and clinical outcomes as well as morbidity and mortality. We compare their outcome to PBMAH patients treated by bilateral adrenalectomy and to CPA patients treated by unilateral adrenalectomy.

Subjects and Methods

Patient cohorts

Patients with adrenal Cushing's syndrome were recruited in four European academic tertiary centers (Medizinische Klinik IV, Munich (n=52), Endocrinology in Charlottenburg, Berlin (n=15), S. Orsola-Malpighi Hospital, Bologna (n=10) and Division of Endocrinology and Diabetes, Department of Internal Medicine I, University Hospital Würzburg (n=8)). German patients were asked to participate in a long-term evaluation within the German Cushing's Registry CUSTODES [14].

Diagnosis was confirmed by chart review with special focus on histology and radiology. All adrenal scans were reviewed in a multidisciplinary tumor board or the original scan was re-reviewed by a radiologist. An original scan was not available in 5 CPA patients, but all 5 patients had the typical histology and long-lasting postoperative adrenal insufficiency of at least 19 month in line with an unilateral CPA. PBMAH was histopathologically defined by the presence of macronodular hyperplasia, whereas unilateral CPAs were specified by single adenomas with atrophic surrounding adrenal tissue. The decision for unilateral adrenalectomy (ADX) in PBMAH was based on several factors which were in most instances analyzed and discussed in a multidisciplinary endocrine patient board: besides imaging characteristics (single adenoma, multiple nodules, atrophic or hypertrophic adrenal cortex) and size differences of the adrenal glands, these decisions were also based on cortisol gradients during adrenal vein sampling [15] and uptake in iodine-131 or [123 I] iodometomidate scintigraphy [16].

Of the 85 patients, 40 were diagnosed with PBMAH, while 45 had unilateral CPAs. Patients who remained without surgery based on personal choice (2 PBMAH, 2 CPA) or had adrenal-sparing subtotal adrenalectomies (4 PBMAH, 4 CPA) were excluded from further analysis. The remaining patients were divided according to surgical procedure in PBMAH with unilateral adrenalectomy (unilat-ADX-PBMAH, n=25), bilateral adrenalectomy (bilat-ADX-PBMAH, n=9), or CPA with unilateral adrenalectomy (unilat-ADX-CPA, n=39).

Clinical studies

Epidemiologic, clinical and biochemical data were extracted from patients' files and entered into an electronic data base. Information on medical history and socio-demographic characteristics were obtained by trained and certified staff members during a standardized patient interview. Moreover, the participants underwent (at least once) a standardized postsurgical medical examination. As part of CUSTODES, the examinations were repeated annually. If not mentioned otherwise, results of the last follow-up are reported. The examination included blood sampling, evaluation of waist-to-hip ratio and quantification of muscle strength and blood pressure. The latter was measured three times on both arms in seated position after 5 minutes of rest. The mean of three measurements was used for statistical analysis. Grip strength was assessed with the Jamar hydraulic hand dynamometer (Sammons Preston, Rolyan). Mean values of three trials of the leading hand were calculated and compared to median values of an age- and gender-matched normative population [17]. For the chair rising test, the time for rising from a chair (height of 45 cm) five times at maximum speed was taken. The patient started while seated and ended while standing. Blood samples were taken in the morning from fasting, seated subjects.

The study was approved by the local ethical committees (Ethikkommission bei der Medizinischen Fakultät der LMU München, Ethikkommission bei der Medizinischen Fakultät der Universität Würzburg, Ethikkommission der Ärztekammer Berlin and ethics

committee of the S. Orsola-Malpighi Hospital of Bologna) and all patients provided written informed consent.

Biochemical measurements

24 hours urinary free cortisol (UFC) was measured with the Liaison Assay (DiaSorin) or with RIA (Immunotech-Assay, Beckman-Coulter). ACTH and serum cortisol were measured with the Liaison Assay (DiaSorin) or with Immulite (Siemens Healthineers). All other biochemical variables were assayed in the central laboratories of the participating centers, using standardized analytical methods.

Definitions

Subjects with blood pressure ≥ 140/90 mmHg, self-reported history of hypertension or intake of antihypertensive medication were classified as hypertensive. Diabetes was defined by HbA1c levels ≥ 6.5% or treatment with antidiabetic drugs. Osteoporosis was defined by T-values ≤-2.5 SD using dual energy X-ray absorptiometry (DXA). Cushing's stigmata included a large variety of symptoms regarded as disease-specific (e.g. moon face, buffalo hump, hirsutism or skin alterations). Muscle weakness was defined by the self-reported disability to rise from knee bending without the aid of arms. Psychiatric morbidities included self-reported anxiety, depression, panic attacks or psychosis. Clinical remission of CS was defined by the disappearance of Cushing's stigmata. Biochemical remission from CS was defined by dependence on glucocorticoid substitution and/or normalization of dexamethasone suppressed serum cortisol (<1.8 µg/dl) and/or normal urinary free cortisol excretion (< 150µg/24h).

Genetic testing

Genetic testing was performed, as previously described [18]. The *ARMC5* coding sequence as well as flanking intronic sequences were amplified by PCR from leukocyte DNA of 11 patients. Both strands of the amplified products were directly sequenced with forward and reverse primers. All mutations were confirmed twice in two independent experiments. The in silico software Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT version 2 (http://sift.jcvi.org/www/SIFT_enst_submit.html) was utilized to predict the pathogenic potential of the missense variants. The software Mutalyser (Version 2.0.3; https://mutalyzer.nl/name-checker/) was utilized to check the sequence variant nomenclature according to Human Genome Variation Society version 2.0.

Quality of life questionnaires

A generic health-related quality of life (QoL) questionnaire (SF-36 Health Survey) [19] and two disease-specific instruments (Tuebingen CD-25 [20] and Cushing QoL [21]) were used for the assessment of QoL. In each of these questionnaires, values can range from 0 to 100. Higher scores in the SF-36 Health Survey as well as the Cushing QoL and lower scores in the Tuebingen CD-25 indicate better QoL.

Statistical analysis

Data were extracted from the German Cushing's Registry CUSTODES. If not stated otherwise, results are expressed as median and interquartile range (IQR). Data between groups were compared using χ^2-Test (2-sided), Mann-Whitney U test or Kruskal-Wallis test. Survival was analyzed using Kaplan-Meier curves. Concerning health-related QoL, Mann Whitney U test was used for comparison of scores between different patient groups. P<0.05 was considered statistically significant. Statistical analysis was performed using SPSS vers. 25 (IBM).

RESULTS

Surgical procedures in patient groups

As summarized in Table 1, clinical and biochemical parameters at initial diagnosis of Cushing's syndrome were comparable between unilat-ADX-PBMAH, bilat-ADX-PBMAH patients and patients with unilat-ADX-CPA except for age at diagnosis. Two out of 10 tested PBMAH patients were found to carry *ARMC5* mutations.

Initial clinical and biochemical outcome following 1st surgery

Unilateral adrenalectomy resulted in clinical and biochemical remission in 21 of the 25 (84%) PBMAH patients. As to be expected, 100% of the bilat-ADX-PBMAH patients and the unilat-ADX-CPA experienced clinical and biochemical remission (Table 2).

Persistence and recurrence of Cushing's syndrome

Adrenalectomy of the contralateral side had to be performed in 3 (12%) of the PBMAH patients initially subjected to unilateral adrenalectomy because of persistent or recurrent hypercortisolism. One patient of the bilat-ADX-PBMAH group developed a (clinically silent) para-aortic tumor 20 years after BADX. This lesion was incidentally detected during CT imaging for a suspected renal carcinoma and surgically resected because of the suspicion of a lymph node metastasis. Histology demonstrated an adrenal marconodule.

Standardized clinical and biochemical evaluation at last follow-up

After a median follow-up of 50 months, 96% of the unilaterally adrenalectomized PBMAH patients were clinically controlled, defined by remission of Cushing's stigmata. In contrast, the percentage of biochemically controlled patients was lower, with 67% having normalized 24h urinary free cortisol (UFC) and 32% having normal cortisol suppression after 1mg dexamethasone. UFC was 1.1-fold the upper limit of normal (= 10% above the reference range) in unilat-ADX-PBMAH (n=13) compared to 0.5-fold in unilat-ADX-CPAs (n=28, $p<0.001$).

Table 3 summarizes clinical and biochemical parameters at follow-up examination in the three patient groups after exclusion of patients who underwent second ADX (n=3) or were lost to follow-up (n=3). According to this analysis, unilat-ADX-PBMAH patients were characterized by elevated midnight salivary cortisol and pathologic dexamethasone suppression test. Clinical outcome was not significantly different compared to bilat-ADX-PBMAH patients and unilat-ADX-CPA patients except for systolic blood pressure.

Adrenal insufficiency and adrenal crisis

Out of 20 unilat-ADX-PBMAH patients 10 (50%) suffered from temporary and 1 (5%) from persistent adrenal insufficiency, while the remaining 9 patients (45%) never experienced adrenal insufficiency (Figure 1). Expectedly, all patients with unilat-ADX-CPA developed adrenal insufficiency (58% temporary and 42% persistent at last follow-up) and all bilat-ADX-PBMAH patients remained adrenal insufficient. Duration of temporary adrenal insufficiency was significantly shorter in unilat-ADX-PBMAH patients compared to patients with unilat-ADX-CPA (median 3 months (IQR 6) vs. 19 months (IQR 45), p=0.002). The daily hydrocortisone replacement dose at last follow-up was not significantly different between bilat-ADX-PBMAH patients and unilat-ADX-CPA patients (median 25mg/d (IQR 15) vs. 20mg/d (IQR 9), p=ns). None of the unilat-ADX-PBMAH patients experienced an adrenal crisis, whereas 38% of the bilat-ADX-PBMAH patients and 8% of the unilat-ADX-CPA patients had one crisis per year on average (p=0.009).

Quality of Life and psychiatric morbidity

QoL at last follow-up was not significantly different between the 3 patient groups except for general health and vitality in the SF-36 questionnaire, which was lowest in the unilat-ADX-CPA patients (Table 4). Similarly, psychiatric morbidity was higher in unilat-ADX-CPA patients (39% vs. 16% in unilat-ADX-PMAH and 0% in bilat-ADX-PBMAH).

Surgical and long term mortality

Surgical 30 day mortality was 0% in all groups. During follow-up, 3 out of the 20 unilat-ADX-PBMAH patients (15%) died. Causes for death were septic shock, sepsis with cardiac decompensation and sudden death of unknown cause (each n=1). All 3 patients had persisting biochemical hypercortisolism at last follow up. In the other two groups (bilat-ADX-PBMAH and unilat-ADX-CPA) no patient died (Figure 2, p=0.008). The last available cortisol level after 1mg dexamethasone was significantly higher in the unilat-ADX-PBMAH patients who died than in surviving patients (15.6 vs. 2.4µg/dl, p=0.014).

DISCUSSION

An increasing number of studies reported on unilateral adrenalectomy in PBMAH patients [9-13,22,23]. These data suggest that unilateral ADX is a safe procedure, which controls hypercortisolism and avoids the risks implied by persistent adrenal insufficiency. However, several caveats have to be taken into account. The number of patients studied is still limited to 7 studies with a total of 81 patients, and most reports were based on monocentric series. Moreover, there are no reference patient groups and long-term mortality has not been reported. These limitations prompted our study, which is multicentric and provides long-term follow-up on important clinical, biochemical and health related quality of life parameters. In addition, the data are compared with outcome data of a closely related entity, cortisol producing adenomas. In terms of severity of Cushing's syndrome at time of diagnosis, our cohorts were well balanced with respect to BMI, blood pressure, diabetes, and biochemical parameters of hypercortisolism.

Novelties of the current analysis

Our study provides substantial new information relevant to patients and physicians. Firstly, clinical outcome data of our series demonstrate that unilateral adrenalectomy in PBMAH patients results in long-term control of Cushing stigmata similar to both control groups, bilaterally adrenalectomized PBMAH patients and unilaterally adrenalectomized CPA patients. Secondly, compared to both control groups, the outcome in unilaterally adrenalectomized PBMAH is *-grosso modo-* similar with respect to metabolic, cardiovascular, health-related QoL, and musculoskeletal parameters. Thirdly, however, a substantial percentage of unilat-ADX-PBMAH patients - in our series 33% (UFC) to 68 % (1 mg dexamethasone test) - keep or re-develop the endocrine phenotype of excessive cortisol secretion. Within this cohort we observed three premature casualties, in part due to infectious complications, which might be interpreted as an indicator of impaired immune function due to hypercortisolism. These patients had less controlled cortisol levels compared to the patients who were still alive at last follow-up.

Outcome of PBMAH in comparison to published series

84% of the unilat-ADX-PBMAH patients in our cohort experienced initial remission. Remission rates previously reported are similar while the overall variability is large (25-93%) [9-11,13]. Contralateral adrenalectomy was performed in 12% of our initially unilaterally adrenalectomized PBMAH patients at a later stage, compared to 0-33% in the literature [9-13].

In contrast to clinical outcome, biochemical outcome was less successful in our series as only 67% had normalized UFC or received glucocorticoid replacement after a median follow-up of 42 months. Normalization of UFC was superior in 2 studies with 86% and 93% after a median follow-up of 53 months and 69 months, respectively [11,13]. Debillon showed normalization of UFC in all cases 3 months postoperatively, but elevation of UFC after 8 years in 13% [10]. Thus, it has to be taken into account that elevation of UFC might re-occur at a later stage after adrenalectomy. In accordance with Lamas [12], we recognized elevated cortisol values after 1mg dexamethasone and disturbed circadian salivary cortisol rhythm in

79% and 67% of cases, respectively. Importantly, abnormalities in circadian cortisol rhythm have been associated with increased risk of cardiovascular morbidity [24].

Occurrence of adrenal insufficiency was similar to the rates in published data. Of the unilat-ADX-PBMAH patients 50% had temporary, and 5% persistent adrenal insufficiency, whereas 45% never experienced adrenal insufficiency. In the literature, the frequencies of adrenal insufficiency range from 7 to 50% (temporary), from 0 to 33% (persistent) and from 50 to 71% (absent) [10-12]. Of note, 38% of the bilat-ADX-PBMAH patients in our series had one adrenal crisis per year on average. On the other hand, long-term outcomes of bilateral adrenalectomy in Cushing's syndrome patients have been shown to be favorable [25].

Postoperative QoL in the SF-36 questionnaire was comparable to the postoperatively improved values of unilat-ADX-PBMAH patients reported by Iacobone [11].

Although severity and duration of hypercortisolism before surgery as well as comorbidities were comparable between uni- and bilateral adrenalectomized PBMAH patients and unilateral adenoma patients, mortality was significantly different. In the group of unilaterally adrenalectomized PBMAH patients 3 died, whereas in the other two groups no death occurred. In the literature mortality has not been reported, especially not compared to other adrenal Cushing entities or different treatment options as bilateral adrenalectomy. We believe that our data indicate that unilaterally adrenalectomized PBMAH patients, while being clinically asymptomatic, are at sustained risk for adverse outcome especially when biochemical parameters of autonomous cortisol secretion are greatly elevated.

Strengths and limitations

The strengths of our study include the multicentric approach, the large number of subjects, the systematic evaluation of Cushing associated comorbidities, and the long follow-up allowing a mortality analysis. The limitations are largely related to the retrospective study design: individual decisions for unilateral or bilateral adrenalectomy did not follow a pre-defined protocol. Some patients were lost to follow-up, and standardized evaluation of outcomes was only possible in a subgroup of patients. Moreover, the group of bilaterally adrenalectomized PBMAH patients was much smaller than the group of unilaterally adrenalectomized PBMAH patients. However, considering the exceptional rarity of this condition, we are convinced that the presented data are robust enough to justify our conclusions.

Conclusions

The present study provides rare data of long-term outcome and mortality of PBMAH patients after adrenalectomy in comparison with a reference patient group. Argumentation for acceptance of mild persistent hypercortisolism against lifelong glucocorticoid dependence is justifiable – as long as it does not lead to enhanced mortality. In view of the presented data, unilateral adrenalectomy should be used with reservation and should be reserved for PBMAH patients with asymmetric hyperplasia or mild cortisol secretion [11]. Although our observational data do not allow to define a 'safe' urinary free cortisol cut-off we believe that persistently elevated levels of more than 2 times upper limit of the norm should lead to additional measures to control hypercortisolism, such as adrenostatic treatment or (subtotal) contralateral adrenal surgery.

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[$]Corresponding author: Martin Reincke, M.D. Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Ziemssenstr. 1, D-80336 Munich, Germany, p: +49 (0)89 44005 2100, f: +49 (0)89 44005 4428, e: martin.reincke@med.uni-muenchen.de

DISCLOSURE STATEMENT
The authors have nothing to disclose.
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Figure 1: Kaplan–Meier analysis on adrenal insufficiency for PBMAH patients after unilateral (unilat-ADX-PBMAH, n=11) or bilateral adrenalectomy (bilat-ADX-PBMAH, n=9) and patients with cortisol-producing adenoma after unilateral adrenalectomy (unilat-ADX-CPA, n=37).

Figure 2: Kaplan–Meier analysis on overall survival for PBMAH patients after unilateral (unilat-ADX-PBMAH, n=20) or bilateral adrenalectomy (bilat-ADX-PBMAH, n=9) and patients with cortisol-producing adenoma after unilateral adrenalectomy (unilat-ADX-CPA, n=38).

Table 1: Clinical and biochemical parameters at diagnosis of Cushing's syndrome (CS) according to the underlying pathology and surgical treatment

	unilat-ADX-PBMAH (n=25)	**bilat-ADX-PBMAH (n=9)**	**unilat-ADX-CPA(n=41)**	
Females / males	16 / 9	5 / 4	35 / 4	
	median (IQR), n	**median (IQR), n**	**median (IQR), n**	**p**
Age at diagnosis in years	56 (22), 25	53 (35), 9	45 (19), 39	0.026
Time from first symptoms to diagnosis in months	22 (27), 15	39 (69), 7	27 (40), 37	ns
Biochemistry				
HbA1c (%)	5.8 (0.7), 19	5.9, 2	5.6 (1.4), 19	ns
UFC (µg/24h)	274 (299), 23	182 (1418), 6	250 (422), 26	ns
Serum cortisol after 1mg DXM (µg/dl)	9 (12), 23	15 (239), 5	15 (16), 33	ns
Midnight salivary cortisol (µg/l)	4 (5), 10	11, 1	4 (6), 21	ns
ACTH (pg/ml)	2.5 (5.0), 21	2.5 (2.5), 7	3.0 (2.9), 27	ns
Clinical evaluation				
Systolic blood pressure (mmHg)	140 (25), 21	140 (43), 5	145 (32), 29	ns
Diastolic blood pressure (mmHg)	88 (11), 21	100 (15), 5	90 (20), 29	ns
BMI (kg/m^2)	27 (8), 22	27 (5), 5	29 (10), 33	ns
	%, n	**%, n**	**%, n**	**p**
Prevalence of Cushing's stigmata	68, 22	86, 7	80, 35	ns

unilat-ADX-PBMAH, unilaterally adrenalectomized PBMAH; bilat-ADX-PBMAH, bilaterally adrenalectomized PBMAH; unilat-ADX-CPA, unilaterally adrenalectomized CPA; PBMAH, Primary bilateral macronodular adrenocortical hyperplasia; CPA, cortisol producing adenoma; UFC, urinary free cortisol; DXM, dexamethasone; BMI, body mass index. Conversion from ACTH in pg/mL to SI units (pmol/L) is performed by multiplication by 0.22

Table 2: Clinical and biochemical outcomes in patients with PBMAH after uni- or bilateral adrenalectomy (unilat-ADX-PBMAH and bilat-ADX-PBMAH) and patients with CPA after unilateral adrenalectomy (unilat-ADX-CPA)

	unilat-ADX-PBMAH n (%)	**bilat-ADX-PBMAH n (%)**	**unilat-ADX-CPA n (%)**	**p**
Initial remission	21/25 (84)	9/9 (100)	39/39 (100)	0.017
Recurrence	3/21 (14)	1/9 (11)*	0/39 (0)	ns
2nd operation necessary	3/25 (12)	1/9 (11)*	0/39 (0)	ns
Remission at last FU (acc. to definition)				
- clinically controlled	22/23 (96)	8/9 (89)	28/38 (74)	ns
- biochemically controlled (UFC)	12/18 (67)	9/9 (100)	30/31 (97)	0.004
- biochemically controlled (DXM)	7/22 (32)	9/9 (100)	30/31 (97)	0.000

* 1992 BADX, 2012 removal of a suspicious partaaortal lymphnode, histologically being an adrenal adenoma
PBMAH, Primary bilateral macronodular adrenocortical hyperplasia; CPA, cortisol producing adenoma; FU, follow-up. Definition: clinically controlled was defined by the remission of Cushing stigmata; biochemically controlled was defined by dependence on glucocorticoid substitution and urinary free cortisol (UFC) <150µg/d or cortisol after 1mg dexamethasone (DXM) < 1.8µg/dl.

Table 3: Clinical and biochemical outcome in patients with PBMAH after uni- or bilateral adrenalectomy (unilat-ADX-PBMAH and bilat-ADX-PBMAH) and patients with CPA after unilateral adrenalectomy (unilat-ADX-CPA) at last follow-up

	unilat-ADX-PBMAH (n=20)	**bilat-ADX-PBMAH** (n=9)	**unilat-ADX-CPA** (n=38)	**p**
Females / males	14 / 6	5 / 4	34 / 4	0.039
	median (IQR), n	**median (IQR), n**	**median (IQR), n**	**p**
Age at last follow-up in years	65 (11), 20	65 (29), 9	55 (24), 38	0.011
Follow-up time since operation in months	50 (100), 20	88 (164), 9	55 (107), 38	ns
Biochemistry at follow-up				

UFC (µg/24h)	117 (133), 13	35, 3	41 (62), 28	0.003
Serum cortisol after 1mg DXM (µg/dl)	2.6 (3.1), 18	0.5, 3	1.0 (0.3), 17	0.000
Midnight salivary cortisol (µg/l)	2.1 (2.3), 8	2.2, 2	0.8 (1.0), 29	0.016
ACTH (pg/ml)	15 (11), 19	13 (38), 8	20 (14), 38	ns
Clinical evaluation at follow-up				
Systolic blood pressure (mmHg)	140 (20), 19	135 (26), 9	119 (26), 38	0.011
Diastolic blood pressure (mmHg)	81 (16), 19	80 (13), 9	78 (12), 38	ns
HbA1c (%)	5.8 (0.8), 19	5.7 (0.9), 8	5.6 (0.6), 38	ns
Total cholesterol (mg/dl)	207 (59), 19	208 (83), 8	200 (47), 38	ns
LDL (mg/dl)	112 (42), 19	122 (45), 7	114 (45), 38	ns
Triglycerides (mg/dl)	94 (84), 19	151 (143), 8	129 (105), 37	ns
Lowest T-value in DXA	-1.7, 3	-0.5, 3	-1.2 (1.6), 23	ns
BMI (kg/m^2)	25.4 (8.6), 20	24.8 (5.7), 9	27.6 (12.0), 38	ns
Waist-to-hip ratio	0.9 (0.1), 9	1.0, 3	0.9 (0.2), 35	ns
Grip strength (%)*	96 (29), 10	100 (29), 6	90 (38), 35	ns
Chair rising test (sec.)	8 (5), 8	9 (5), 6	8 (4), 32	ns

* Grip strength was assessed with a hand dynamometer; mean values of three trials of the leading hand were compared to median values of an age- and gender-matched normative population (=100%).
PBMAH, Primary bilateral macronodular adrenocortical hyperplasia; CPA, cortisol producing UFC; urinary free cortisol; DXM, dexamethasone; DXA, dual energy X-ray absorptiometry; BMI, body mass index

Table 4: Health-related quality of life (QoL) at last follow-up in patients with PBMAH after uni- or bilateral adrenalectomy (unilat-ADX-PBMAH and bilat-ADX-PBMAH) and patients with CPA after unilateral adrenalectomy (unilat-ADX-CPA) at last follow-up

Females and males	**unilat-ADX-PBMAH**	**bilat-ADX-PBMAH**	**unilat-ADX-CPA**	
	median (IQR), n	**median (IQR), n**	**median (IQR), n**	**p**
SF-36 Physical functioning	78 (58), 6	88 (35), 4	68 (41), 18	ns
SF-36 Role-physical	63 (100), 6	88 (81), 4	0 (63), 18	ns
SF-36 Bodily-pain	61 (51), 6	63 (36), 4	44 (56), 18	ns
SF-36 General health	40 (30), 6	68 (30), 4	33 (26), 18	0.032
SF-36 Vitality	45 (39), 6	58 (19), 4	28 (28), 18	0.031
SF-36 Social functioning	57 (34), 6	94 (31), 4	38 (56), 18	ns
SF-36 Role-emotional	33 (75), 6	84 (59), 4	50 (100), 18	ns
SF-36 Mental health	50 (28), 6	86 (25), 4	52 (40), 18	ns
Cushing QoL	64 (52), 6	79 (35), 4	44 (24), 18	ns
Tuebingen CD-25 Total Score	22 (34), 6	15, 3	33 (30), 17	ns
	n (%)	**n (%)**	**n (%)**	**p**
Psychiatric morbidity	3/19 (16)	0/9 (0)	15/38 (39)	0.042

PBMAH, Primary bilateral macronodular adrenocortical hyperplasia; CPA, cortisol producing adenoma; SF-36, Short Form (36) Health Survey: higher scores indicate better QoL; Cushing QoL: higher scores indicate better outcome; Tuebingen CD-25: lower scores indicate better QoL